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Health and Environmental Effects Profile for Methyl Isocyanate

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16. ABSTRACT

The Health and Environmental Effects Profile for Methyl Isocyanate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine a Reference Dose (RfD) or a carcinogenic potency factor for methyl isocyanate.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR METHYL ISOCYANATE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati. The staff of the Environmental Criteria and Assessment Office in Research Triangle Park provided extensive assistance in the preparation of this document.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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EXECUTIVE SUMMARY

Methyl isocyanate is a colorless liquid at ambient temperatures (Hawley, 1981) that decomposes in water, alkali or acid, and is susceptible to polymerization (U.S. EPA-NIH, 1986). It is used as a chemical intermediate for the production of carbamate insecticides and herbicides (U.S. EPA-NIH, 1986). Currently, three U.S. companies (Union Carbide, DuPont and FMC Corp.) manufacture methyl isocyanate (SRI, 1986). It has been estimated that 27-30 million pounds of methyl isocyanate were produced in the United States in 1975; the 1980 production was expected to reach ~50 million pounds (Chadwick and Cleveland, 1981). The 1983 production was estimated at 6.8-12 million kilograms. The current production volume for methyl isocyante is not available.

In water, hydrolysis will be the dominant environmental fate process for methyl isocyanate. Based on experimentally determined rate constants (Castro et al., 1985), the uncatalyzed aqueous hydrolysis half-lives at 15 and 25°C are ~20 and 9 minutes, respectively. Relatively minor amounts of methyl isocyanate may volatilize from water, but volatilization is not expected to be competitive with hydrolysis. Aquatic adsorption and bioconcentration are not expected to be important. In the atmosphere, methyl isocyanate will react in the vapor-phase with photochemically produced HO radical at an estimated half-life of 3.22 months (U.S. EPA, 1986a). The hydrolysis reaction in moist air is expected to be much slower than in water. In soil, hydrolysis (in moist soils) and volatilization (from dry soil surfaces) are expected to be important fate processes.

Based on preliminary results (as of September, 1985) of the National Occupational Exposure Survey, it has been estimated that 1821 U.S. workers

are potentially exposed to methyl isocyanate (NIOSH, 1985). Ambient water or air monitoring data regarding methyl isocyanate could not be located in the available literature as cited in the Appendix. Extensive data documenting human exposure following the accidental release of methyl isocyanate in Bhopal are available and discussed in the text.

Pertinent data regarding effects of methyl isocyanate on aquatic organisms could not be located in the available literature as cited in the Appendix.

Pertinent data regarding the pharmacokinetics of methyl isocyanate are limited. Some reports of the accident in Bhopal, India, indicated that urinary thiocyanate levels of survivors were elevated (Salmon et al., 1985). Since cyanide is converted to thiocyanate in vivo (U.S. EPA, 1985), increased thiocyanate levels following exposure to methyl isocyanate would indicate that cyanide was a metabolite. Salmon et al (1985), however, demonstrated that rats exposed by inhalation to methyl isocyanate excreted less thiocyanate in the urine than did air-exposed rats.

Pertinent data regarding the chronic or subchronic toxicity or oncogenicity of methyl isocyanate were not available. Extensive recent data are available concerning the effects of acute inhalation exposure in both humans and experimental animals. NTP (1983) found the compound not to be mutagenic in a standard reverse mutation assay, nor in a sex-linked recessive lethal test in Drosophila. In contrast, dose-related increases in sister chromatid exchange (SCE) and chromosome aberrations (CA) were seen in Chinese hamster ovary cells. These increases were accompanied by cytotoxicity. A dose-dependent increase in the frequency of mutants in L5178Y cells was observed (also accompanied by cytotoxicity). Small increases in SCE and CA have been noted in mouse bone marrow following inhalation exposure to methyl isocyanate.

Methyl isocyanate was apparently the chief etiological agent in the deaths of ~2000 people after a gas leak at a Union Carbide facility in Bhopal, India. Most of the fatalities were caused by pulmonary edema, and many survivors had symptoms of chronic lung disease (Sax, 1985). Corneal irritation was also consistently observed, but was often reversible in survivors. Other toxic manifestations in fatal cases were bright red blood, softening of the brain tissue and early rigor mortis. Indian physicians claimed that ~600 of the deaths were atypical as they were characterized by exceptionally bright red blood and absence of a panic reaction, pulmonary edema or signs of struggle (Browning, 1985a). Survivors of the Bhopal accident also suffered reproductive impairments, including leukorrhea, pelvic inflammatory disease, excessive menstrual bleeding, suppression of lactation, increases in stillbirths and spontaneous abortions, and male impotence.

In addition to the severe mucous membrane irritation, isocyanates (as a class) act as pulmonary sensitizers (Karlsson et al., 1985; Chadwick and Cleveland, 1981). Short-term exposure to a concentration of 4.7 mg/m^3 was weakly irritating to volunteers, whereas 49.5 mg/m^3 was intolerable (Karlsson et al., 1985).

Results of acute inhalation experiments on laboratory animals have consistently shown pulmonary edema and upper respiratory tract damage after exposure to methyl isocyanate (Union Carbide, 1981; Dodd and Eisler, 1983; Salmon et al., 1985; Nemery et al., 1985; Kimmerle and Eben, 1964; Dodd et al., 1982). Rats exposed 6 hours/day for 8 days to 3 ppm (7 mg/m^3) methyl isocyanate had significant increases in relative lung, kidney and testicular weights, and decreased liver weights, submucosal fibroplasia of the bronchi, pneumonitis, alveolar mucous, repair of the immature fibroblasts, squamous metaplasia of the respiratory epithelium and delayed death (Union Carbide, 1981; Dodd and Eisler, 1983).

Rats exposed to 65 ppm (152 mg/m³) for 2 hours were moribund or died within 50 days of exposure, and rats exposed to 11 or 21 ppm (26 or 49 mg/m³) had pronounced narcosis (Salmon et al., 1985). Exposure of rats to 1 mg/ℓ (1000 mg/m³) for 1 hour resulted in destruction of Type I pneumocytes, alveolar edema and hemorrhage (Nemery et al., 1985). Exposure to 0.1-0.5 mg/ℓ (100-500 mg/m³) for 1 hour resulted in necrosis and autophagy of the upper airways.

Oral and dermal LD_{50} values in experimental animals have ranged from 68-140 and 210-1800 mg/kg, respectively (Smyth et al., 1969; Vernot et al., 1977). Inhalation 6-hour LC_{50} values in rats, mice and guinea pigs vary from 5.4-12.2 ppm (12.6-28.5 mg/m³) (Dodd et al., 1982). The potent antisickling properties of methyl isocyanate were demonstrated by Lee (1976).

The lack of carcinogenicity and subchronic and chronic toxicity data for methyl isocyanate precludes the derivation of an RfD, RQ, q_1^* or F factor. Because carcinogenicity data in animals and humans are not available and therefore inadequate, methyl isocyanate is classified as an EPA Group D chemical.

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LIST OF ABBREVIATIONS

CAS	Chemical Abstract Service
K_{ow}	Log octanal/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
PEL	Permissible exposure level
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
TLV	Threshold-limit value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Methyl isocyanate is the common name for methane, isocyanato-, as currently designated by the CAS. Synonyms include methylcarbylamine, methylcarbonimide and isocyanic acid, methyl ester. The structure, molecular weight, empirical formula and CAS Registry number for methyl isocyanate are as follows:

$$CH_3\text{-}N{=}C{=}O$$

Molecular weight: 57.05

Empirical formula: C_2H_3NO

CAS Registry number: 624-83-9

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Methyl isocyanate is a colorless liquid at ambient temperatures (Hawley, 1981). Selected physical properties are listed below:

Melting point:	-45°C	Weast, 1985
Boiling point: (760 mm Hg)	39.1°C	Union Carbide, 1979
Specific gravity:	0.9599 (20/20°C)	Union Carbide, 1979
Refractive index: (18°C)	1.3419	Weast, 1985
Vapor pressure:		
at 20°C	348 mm Hg	Union Carbide, 1979
at 25°C	477 mm Hg	Amoore and Hautala, 1983
Water solubility:		
at 20°C	reacts	Union Carbide, 1979
Log K_{ow}:	not relevant	
Flash point:	-7°C (closed cup)	U.S. EPA/NIH, 1986
Autoignition temperature:	535°C	U.S. EPA/NIH, 1986
Air odor threshold:	2.1 ppm	Amoore and Hautala, 1983

In general, compounds that have active hydrogen atoms (alcohols, amines, acids, urea derivatives) react with methyl isocyanate (U.S. EPA/NIH, 1986). Methyl isocyanate decomposes in water, alkali or acid and is susceptible to polymerization. The polymerization becomes rapid in the presence of zinc, iron, tin, copper and their salts, and other catalysts.

Methyl isocyanate reacts with water to yield CO_2, methylamine, dimethylurea or trimethylbiuret, accompanied by evolution of heat, which causes evaporation of the isocyanate (U.S. EPA/NIH, 1986). The reaction is relatively slow at <20°C, but becomes violent at higher temperatures or in the presence of acid or bases. Methyl isocyanate is highly flammable (Hawley, 1981). Although methyl isocyanate reacts with water, its solubility in water has been reported to be 100 g/ℓ at 15°C (U.S. EPA/NIH, 1986).

1.3. PRODUCTION DATA

The current U.S. manufacturers of methyl isocyanate are DuPont in LaPorte, TX, and FMC Corp. and Union Carbide in Institute, WV (SRI, 1986). In late 1984, during the Bhopal, India accident, when release of methyl isocyanate killed >2500 people, Union Carbide was the only U.S. manufacturer of methyl isocyanate (Anonymous, 1985a). The current FMC Corporation production unit for methyl isocyanate is near the Union Carbide facility that was supplying FMC with methyl isocyanate for the synthesis of carbofuran (Anonymous, 1985b). DuPont's methyl isocyanate production facility began operation in 1985; DuPont previously purchased methyl isocyanate from Union Carbide (Anonymous, 1985c).

Union Carbide has produced methyl isocyanate by reacting phosgene with methylamine according to the following general reaction (Soder, 1976):

$$CH_3NH_2 + COCl_2 \rightarrow CH_3NCO + 2HCl$$

DuPont manufactures methyl isocyanate in a "close coupled" process in which air and monomethyl formamide react at 550-650°C to form methyl isocyanate

and water (Anonymous, 1985c). The water is separated out and the methyl isocyanate is converted directly into the pesticide methomyl.

It has been estimated that 12-14 million kilograms of methyl isocyanate were produced in the United States in 1975; the 1980 production was expected to reach ~50 million pounds (Chadwick and Cleveland, 1981); however, current production volumes were not available. The USITC (1984) estimated that 6.8-12 million kilograms were manufactured in 1983. Production data available from the public portion of the U.S. EPA TSCA Production File for 1977 are listed in Table 1-1.

1.4. USE DATA

Methyl isocyanate is used as a chemical intermediate for the production of carbamate insecticides and herbicides (U.S. EPA/NIH, 1986). Consumption for these pesticides has been estimated as follows (U.S. EPA/NIH, 1986): carbaryl, 60%; carbofuran, 25%; methomyl, 10%; aldicarb and its sulfone, 4%; other pesticides, 1%. Methyl isocyanate can also be used as a general chemical intermediate (U.S. EPA/NIH, 1986).

1.5. SUMMARY

Methyl isocyanate is a colorless liquid at ambient temperatures (Hawley, 1981) that decomposes in water, alkali or acid, and is susceptible to polymerization (U.S. EPA/NIH, 1986). It is used as a chemical intermediate for the production of carbamate insecticides and herbicides (U.S. EPA/NIH, 1986). Currently, three U.S. companies (Union Carbide, DuPont and FMC Corp.) manufacture methyl isocyanate (SRI, 1986). It has been estimated that 27-30 million pounds of methyl isocyanate were produced in the United States in 1975; the 1980 production was expected to reach ~50 million pounds (Chadwick and Cleveland, 1981). The current production volume for methyl isocyante is not available.

TABLE 1-1

Production Data for Methyl Isocyanate in 1977*

Producer/Location	Manufacturer/Importer	Production Range
Union Carbide Institute, WV	manufacturer	confidential
Story Chemical Corp. North Muskegon, MI	manufacturer	10-100 thousand pounds
Mobay Chemical Corp. Pittsburgh, PA	importer	confidential

*Source: U.S. EPA, 1977

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Castro et al. (1985) experimentally determined the following rate constants for the uncatalyzed aqueous hydrolysis of methyl isocyanate:

Temperature (°C)	Rate Constant (sec^{-1})
15	0.00059
25	0.00134
35	0.00335
45	0.00755

Based on the rate constants above, the hydrolysis half-lives at 15° and 25°C would be ~20 and 9 minutes, respectively. The hydrolysis of methyl isocyanate is a two-stage reaction (Castro et al., 1985), which may be represented as follows:

$$CH_3NCO + H_2O \rightarrow CH_3NHCO_2H$$

$$CH_3NHCO_2^- + H^+ \rightarrow CH_3NH_2 + CO_2$$

Depending on the conditions, there can also be some reaction of the amine product with the reactant:

$$CH_3NCO + CH_3NH_2 \rightarrow CH_3NCONHCH_3$$

Therefore, the hydrolysis products may include N-carboxymethylamine, methylamine, carbon dioxide and N,N'-dimethylurea. Castro et al. (1985) also found hydrolysis to be acid-catalyzed.

Tiger et al. (1971) examined the kinetics of methyl isocyanate hydrolysis in aqueous dioxane at various temperatures and water concentrations. Extrapolation of the data to 100% water hydrolysis yields rate constants similar to those of Castro et al. (1985).

The hydrolysis half-lives of ~20 and 9 minutes at 15 and 25°C, respectively, indicate that hydrolysis will be the dominant fate mechanism in water.

2.1.2. **Oxidation.** Pertinent data regarding the oxidation of methyl isocyanate could not be located in the available literature as cited in the Appendix.

2.1.3. **Photolysis.** Pertinent data regarding the photolysis of methyl isocyanate could not be located in the available literature as cited in the Appendix.

2.1.4. **Microbial Degradation.** Pertinent data regarding the microbial degradation of methyl isocyanate could not be located in the available literature as cited in the Appendix.

2.1.5. **Volatilization.** Based on a vapor pressure of 250 mm Hg at 15°C (estimated from data at 20 and 25°C; see Section 1.2.) and a water solubility of 100 g/ℓ (U.S. EPA/NIH, 1986), the Henry's Law constant for methyl isocyanate can be estimated to be ~1.9×10^{-4} atm/m³-mol at 15°C. A Henry's Law constant of this magnitude indicates that volatilization would normally be significant from all bodies of water (Lyman et al., 1982). Using the method of Lyman et al. (1982), a volatilization half-life of 5.6 hours can be estimated from a river 1 m deep, flowing at a speed of 1 m/sec with a wind velocity of 3 m/sec. The hydrolysis half-life of ~20 minutes at 15°C (see Section 2.1.1.), however, indicates that volatilization will not be competitive with hydrolysis.

2.1.6. **Adsorption.** Adsorption of methyl isocyanate to particulate organic matter and sediment in water is not expected to be significant since it hydrolyzes rapidly in water and is water soluble (100 g/ℓ at 15°C).

2.1.7. Bioconcentration. Bioaccumulation of methyl isocyanate in aquatic organisms is not expected to be significant since it hydrolyzes rapidly in water and is water soluble (100 g/ℓ at 15°C).

2.2. AIR

Experimental data pertaining to the fate of methyl isocyanate in the atmosphere could not be located in the available literature as cited in the Appendix. Because of its high vapor pressure, methyl isocyanate released to the atmosphere is expected to exist in the vapor-phase and not be associated with particulate matter. The half-life for the vapor-phase reaction of methyl isocyanate with photochemically produced HO radical in the atmosphere has been estimated to be 3.22 months at 25°C (U.S. EPA, 1986a), assuming an atmospheric HO radical concentration of 8×10^5 molecules/m^3. Since methyl isocyanate hydrolyzes rapidly in water, hydrolysis of this compound in moist air is possible. Fishbein (1979) showed that the hydrolysis half-life of bis(chloromethyl)ether in air is >1000 higher than in water. Therefore, methyl isocyanate may not hydrolyze in moist air for days and may persist in the atmosphere.

2.3. SOIL

Hydrolysis and volatilization are expected to be the important fate processes in soil. Under moist conditions, methyl isocyanate will hydrolyze at a rate that will be at least as fast as it would be hydrolyzed in pure water at the same temperature. In dry soil, methyl isocyanate is expected to evaporate rapidly from soil surfaces, since it has a relatively high vapor pressure.

2.4. SUMMARY

In water, hydrolysis will be the dominant environmental fate process for methyl isocyanate. Based on experimentally determined rate constants (Castro et al., 1985), the uncatalyzed aqueous hydrolysis half-lives at 15 and 25°C are ~20 and 9 minutes, respectively. Relatively minor amounts of methyl isocyanate may volatilize from water, but volatilization is not expected to be competitive with hydrolysis. Aquatic adsorption and bioconcentration are not expected to be important. In the atmosphere, methyl isocyanate will react in the vapor-phase with photochemically produced HO radical at an estimated half-life of 3.22 months (U.S. EPA, 1986a). The hydrolysis reaction in moist air is expected to be much slower than in water. In soil, hydrolysis (in moist soils) and volatilization (from dry soil surfaces) are expected to be important fate processes.

3. EXPOSURE

3.1. WATER

Data pertaining to methyl isocyanate in ambient water could not be located in the available literature as cited in the Appendix. The U.S. EPA (1986b) STORET database contained no postings for the compound.

Methyl isocyanate may be released in wastewater effluents generated by its commercial production and use. Methyl isocyanate, however, hydrolyzes rapidly in water (see Section 2.1.1.); therefore, it is not surprising that it has not been detected in the ambient aquatic environment.

3.2. FOOD

Pertinent monitoring data regarding methyl isocyanate in food could not be located in the available literature as cited in the Appendix.

3.3. INHALATION

Data regarding methyl isocyanate in ambient air could not be located in the available literature as cited in the Appendix. Release of methyl isocyanate to the air may occur from fugitive emissions and leaks at its commercial production, use and storage sites. The EPA has reported that between 1980 and 1984, 28 leaks of methyl isocyanate occurred at the Union Carbide facility in Institute, WV (Dwyer and Gibson, 1985).

Limited information was found on the environmental release of or exposure to MIC, except for accidental release at Bhopal, India and at Institute, West Virginia. On December 3, 1984, an MIC storage tank at a Union Carbide pesticide manufacturing plant in Bhopal overheated and blew open safety valves, releasing up to 36 metric tons of MIC as a vapor in a foglike cloud (Heylin, 1985). Union Carbide reported that analysis of products and experimental simulation indicated that 120-240 gallons of water had entered the tank and initiated the reaction (Browning, 1985b). Although

Union Carbide's procedures for handling, shipping, storage, and use take into account the hazardous nature of MIC (Worthy, 1985), equipment designed to prevent such release failed to work properly in Bhopal, including tank refrigeration, vent gas scrubbers, and a flare tower (Lepkowski, 1985a). In Bhopal prior to December 2, 1984, a number of major leaks had occurred. These include: 1) a naphtha storage fire ignited by welding sparks on November 24, 1978, resulting in the hospitalization of 47 persons and a damage estimate of $650,000; 2) liquid phosgene spilled from a pipeline onto a worker opening line flanges on December 24, 1981, resulting in the death of the worker the following day; 3) phosgene leak from pumps affecting 25 persons of which 16 were hospitalized on February 10, 1982; and 4) a mixture of MIC, chloroform, phosgene and hydrogen chloride leaked from a pipe valve on October 6, 1982, in which 3 people were burned and 15 suffered eye or throat irritation. In addition, three minor accidents were reported that resulted in chemical burns on the limbs of workers (Dave, 1985).

The accidental release of MIC in Bhopal on December 3, 1984, exposed ~200,000 people in a 12-km^2 area, south-southeast of the MIC plant. MIC at the plant was used primarily to make Sevin or carbaryl. Sevin had not been produced at the plant since October 22, 1984, and three storage tanks contained ~37, 39 and 0.91 metric tons of MIC, respectively. At 8:30 p.m. on December 2, 1984, the night shift workers started washing the filter pressure safety valves of the MIC storage tanks. At 9:30 p.m., a pressurized water hose was connected to the pipeline. By 11:00 p.m., the pressure had risen to 10 psig. At 12:15 a.m., the pressure rose to 12 psig and the plant supervisor was summoned. Before he arrived, the pressure gauge reached the maximum on the gauge, 55 psig. By 1:00 a.m., MIC vapors were detected on the ground and employees activated the alarm with messages being

sent to police, the fire brigade, and the works manager. By 1:45 a.m., the MIC discharge had stopped and the air in the plant was clear. Thus, in 40-60 minutes, ~23-27 metric tons of MIC were vaporized or decomposed and released into the atmosphere. Of the 100 workers at the plant, only one was affected, and he was not seriously injured. The magnitude of the release was affected by the following: 1) the shutdown of the refrigeration system for the MIC storage tanks; 2) the caustic soda scrubber was initially nonfunctional, but even when functional the amount of sodium hydroxide was incapable of neutralizing the large quantity of gases and vapors; 3) the flare unit was disconnected and the pilot flame was shut off; and 4) the atmosphere was stable with a diurnal inversion that helped maintain cloud close to ground level. No atmospheric measurements of MIC were taken but the concentration of MIC has been reconstructed from estimates based on effects to plant and animal life and the number of human deaths in various regions of the city of Bhopal and on the meteorological conditions. As the cloud spread through the city, estimated MIC levels of 13, 17 or 26 ppm were determined for inversion depths of 100, 75 or 50 m, respectively. It is quite likely that concentrations of up to 100 ppm for a period of 30 minutes were experienced around the plant area (Lepkowski, 1985a,b; Dave, 1985).

In addition to the release of MIC and recognized thermally generated by-products, a controversy over the release of cyanide developed. Union Carbide officials have continued to deny that cyanide was released, however, 3 days after the MIC release, scientists of India's Air Pollution Control Board detected cyanide at the MIC storage tank area and up to 50 m downwind (Lepkowski, 1985b). Near the MIC storage tank cyanide levels were 4.5 mg/m^3 on December 6, 1984, and at 50 m from the tank, cyanide levels were 2.5 mg/m^3; however, no cyanide was detected at any of five sampling sites

in the city of Bhopal (Dave, 1985). The presence of cyanide at the MIC storage tank is controversial, since the release of MIC and its byproducts was from the scrubber, some 600 ft from the tank (Lepkowski, 1985b).

A special U.S. EPA investigation of Union Carbide's records (prompted by the Bhopal incident) also identified 28 leaks of MIC gas from three underground storage tanks in Institute, WV, between 1980 and 1984 (Worthy, 1985). One leak may have involved up to 380 kg in a solution of 6400 kg of chloroform (Peterson, 1985). At least 10 other releases involved more than 0.454 kg of which 8 may have been ground spills (Long and Hanson, 1985). Union Carbide later revised these estimates and reported that none of the spills exceeded 0.454 kg (Browning, 1985b). Since the U.S. EPA investigation, Union Carbide reported 62 MIC leaks and 22 MIC/phosgene leaks, apparently all smaller than the U.S. EPA reporting requirement of 0.454 kg.

MIC has been found in the smoke from several types of cigarettes (Philippe and Honeycutt, 1965); thus, traces of the compound are released into the environment from cigarette smoke. Although about 1-5 ppm of MIC are present in the smoke, a smoker receives an approximate dose of only 4 μg of the isocyanate per cigarette (Wynder and Hoffmann, 1967). In comparison to this exposure, a worker exposed to the 8-hour TLV of 0.02 ppm could retain as much as 500 μg.

Estimates of occupational exposure to MIC have been reported in industrial hygiene surveys performed by the National Institute for Occupational Safety and Health (NIOSH). According to the National Occupational Hazard Survey (NOHS, 1970), ~5366 workers were potentially exposed to MIC in domestic workplace environments in 1970. Preliminary data from the National Occupational Exposure Survey (NOES) for 1980 indicate that 1821 workers, including 273 women, were exposed to MIC.

3.4. DERMAL

Pertinent monitoring data regarding dermal exposure to methyl isocyanate could not be located in the available literature as cited in the Appendix.

3.5. SUMMARY

Based on preliminary results (as of September, 1985) of the National Occupational Exposure Survey, it has been estimated that 1821 U.S. workers are potentially exposed to methyl isocyanate (NIOSH, 1985). Ambient water or air monitoring data regarding methyl isocyanate could not be located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

Pertinent data regarding the pharmacokinetics and metabolism of methyl isocyanate are very limited. Salmon et al. (1985) stated that some studies on the methyl isocyanate accident in Bhopal, India, reported that urinary thiocyanate levels of survivors of the incident were elevated. Since cyanide is converted to thiocyanate *in vivo* (U.S. EPA, 1985), the finding of increased thiocyanate levels in survivors suggests that cyanide is an intermediate in the metabolism of methyl isocyanate. The first autopsies conducted after the accident indicated cyanide poisoning. Within a week or so, sodium thiosulfate was being administered to surviving patients. Following administration, urinary thiocyanate levels rose to 2-2.5 mg compared with 0.03-0.2 in controls (Dave, 1985). In addition, some toxicological effects were surprisingly similar to cyanide poisoning (Dave, 1985). Even after a time when no further direct cyanide exposure was possible, the "cyanide-like" symptoms were still present and sodium thiosulfate treatment continued to be successful (Lepkowski, 1985b). After considerable deliberation, it was shown that reactions involving the "cyanogen pool" and biochemical by-products of MIC accounted for the success of the sodium thiosulfate treatment. At least one scheme of how MIC could lead to cyanide formation has been postulated (Lepkowski, 1985b). At this point the cyanide controversy has not been resolved and has become an important political issue. To test this hypothesis, Salmon et al. (1985) exposed male hooded Lister rats by inhalation to 65 ppm (152 mg/m^3) methyl isocyanate for 2 hours and measured urinary thiocyanate excretion for 24 hours. The exposed rats excreted ~6.4 times less thiocyanate than did air-exposed controls, indicating that cyanide was not a metabolite. Salmon et al. (1985)

suggested that the unexpected decrease in thiocyanate excretion in the methyl isocyanate-exposed rats was due to an inhibition of general intermediary metabolism and food intake. They further suggested three possible explanations for increased thiocyanate levels in the Bhopal survivors: an over-compensation in response to the inhibition of thiocyanate metabolism by methyl isocyanate exposure; another environmental contaminant or dietary source of cyanide; or another source of cyanide released during the accident. The data were insufficient to distinguish among the possibilities.

It should be noted that there was no indication of cyanide involvement or that sodium thiosulfate ameliorated MIC toxicity in animal studies conducted by Jameson et al. (1986). Alarie et al. (1986) investigated a possible cyanide effect induced by MIC by exposing guinea pigs to MIC (37 ppm for 3 hours). There was no evidence of inhibition of oxygen utilization despite a reduction in minute ventilation.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of methyl isocyanate could not be located in the available literature as cited in the Appendix. The National Toxicology Program has selected methyl isocyanate for general toxicity testing (NTP, 1986).

5.2. MUTAGENICITY

While currently only abstracts of mutagenicity studies on MIC conducted by NTP have appeared in the literature (Kligerman et al., 1986; Shelby et al., 1986), the complete results have been accepted for publication (Caspery and Myhr, 1986; Mason et al., 1986; Tice et al., 1986). Negative responses were obtained in a Salmonella preincubation assay using five tester strains and in sex-linked recessive lethal tests in Drosophila exposed to MIC by feeding, injection and inhalation. Reproducible dose-related increases were observed for both SCEs and CAs in Chinese hamster ovary cells. These increases were accompanied by significant cell cycle delay and cytotoxicity. A dosedependent increase in the frequency of mutants at the thymidine kinase locus in L5178Y cells was also observed. This test was conducted only without exogenous S-9 activation and the increases in mutant frequency were also accompanied by cytotoxicity.

Cell cycle time, micronuclei and SCE in bone marrow and peripheral blood lymphocytes and chromosome aberrations determinations were made in B6C3F1 mice following single 2 hour (3, 10, 30 ppm) and multiple 6 hours/day, 4-day (1, 3, 6 ppm) inhalation exposures. Cell cycle time was increased in proliferating bone marrow cells and there were small, exposure-related increases in both SCEs and CA frequencies.

Another inhalation study conducted at the University of Pittsburgh (Conner et al., 1986) in B6D2F1 mice reported similar findings, i.e., cell cycle delay and marginal increases in SCE.

5.3. TERATOGENICITY

Two recent studies have been conducted to evaluate the reproductive toxicity of MIC. Varma et al. (1986) exposed pregnant Swiss-Webster mice on day 8 or 14 of gestation to 0, 2, 6, 9 or 15 ppm MIC for 3 hours. For animals exposed to 9 or 15 ppm, a decrease in maternal body weight gain, death in 14% of the dams, and complete resorption of the litter in 75% of the exposed dams were noted. In addition, placental weights, fetal body weights, and skeleton sizes were decreased without signs of significant external or internal organ abnormalities. When exposed on day 14 of gestation, MIC was more toxic (64% mortality) than on day 8 of gestation (14% mortality). These effects were much less pronounced following three exposures to 2 or 6 ppm MIC. Exposure to 9 ppm MIC adversely affected the estrus cycle and the fertility of both male and female mice. Schwetz et al. (1986) studied the effects of MIC on reproduction and late pregnancy in CD-1 mice exposed 6 hours/day during gestation days 14-17 to 0, 1 or 3 ppm MIC. Decreased live litter size at birth and decreased neonatal survival was noted during lactation. Maternal survival and maternal and neonatal body weights were unaffected. There was no significant increase in fetal resorptions that would imply a dominant-lethal effect in untreated females mated to MIC-exposed males; no effect on male fertility was noted. Similarly, no effects were noted in the reproductive capacity of male and female mice undergoing mating trials during the first and eighth weeks following exposure.

5.4. OTHER REPRODUCTIVE EFFECTS

After the Bhopal accident (Section 5.6.) in which ~2000 people died from acute exposure to methyl isocyanate, an unusually high percentage of survivors had disorders of the reproductive system (Sax, 1985). These disorders in women, when measured 3 months after the accident, included leukorrhea (94%), pelvic inflammatory disease (79%), excessive menstrual bleeding (46%) and suppression of lactation (57%). Other deleterious effects included increases in the number of stillbirths and spontaneous abortions as well as increased frequency of male impotence. Appropriate background rates for these disorders were not provided.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Pertinent data regarding the chronic and subchronic toxicity of methyl isocyanate could not be located in the available literature as cited in the Appendix.

5.6. OTHER RELEVANT INFORMATION

Methyl isocyanate was presumably the agent chiefly responsible for the deaths of ~2000 people and adverse health effects in $\geq$170,000 survivors (Sax, 1985) after a Union Carbide company gas leak in Bhopal, India. Virtually all victims had eye problems and emesis, and pulmonary edema was the probable cause of death in most cases. In addition, most dead victims had very bright red blood (which was also observed in the heart and brain), softening of brain tissue and early rigor mortis. Many survivors had symptoms of chronic lung disease, including fibrosis, emphysema and bronchitis.

Verbal reports by Indian physicians, subsequent to the accident, revealed that ~600 fatalities were characterized by an apparently peaceful death, absence of cyanosis, absence of pulmonary edema and venous blood brighter red than expected (Browning, 1985a). Browning (1985a) attributed

these deaths to factors other than methyl isocyanate-induced lung irritation. In addition, the possibility that cyanide gas from an independent source may have been released during the leak has been raised (Sax, 1985; Salmon et al., 1985).

Following the initial insult, many deaths resulted from secondary respiratory infections such as bronchitis and bronchial pneumonia. Other respiratory effects that have persisted include coughing, shortness of breath, and extreme fatigue (Lepkowski, 1985b). More than 300 postmortem examinations were performed. The most striking changes are as follows: 1) lung weights were 2-3 times higher than normal; 2) the lung was reddish in color (indicating hemorrhage); and 3) the respiratory tract showed tracheitis, bronchitis, pulmonary edema and bronchopneumonic changes (Dave, 1985). Of the 150,000 affected, reduction in lung function was noted as follows: 1) 27% exhibited a reduction in vital capacity to 55-60%; 2) 55% showed impaired oxygen uptake rates; 3) 43% exhibited central airway obstruction; 4) 59% exhibited respiratory alkalosis; and 5) 23% showed abnormally low oxygen pressure in blood gases (Dave, 1985). In addition, chest X-rays were normal in only 5%, 30% had fibrosis of the lung, and lavage studies showed high neutrophil counts in the lung (Dave, 1985). In a followup study, Kamat et al. (1985a) studied 82 subjects with persistent symptoms. Radiologically, there was evidence of interstitial fibrosis that had not improved in the 6 weeks following exposure. In contrast, lung function and blood gas studies showed some improvement in pO_2 during this period. In a later report, Kamat et al. (1985b) studied 113 survivors at 3 and 6 months following the accident. Clinically, several subjects improved except for dyspnea (breathlessness), weakness, poor memory, cough, and chest pain. Flow volume studies continue to indicate airway abnormalities. Only

15-20% have shown remarkable improvement in airway obstruction. Histologically, three patients showed peribronchial and endobronchial fibrosis, interstitial infiltrates, bronchiolitis, and septal and pleural thickening. These findings confirm that long-term effects from MIC can result from a single exposure. These studies are continuing in order to evaluate if the fibrosis leads to progressive disease or eventual regression.

Severe eye damage was recorded in 1025 persons; 99% of the persons treated in the early days following the accident complained of a burning sensation in the eyes and excessive lacrimation (Dave, 1985). Of those severely affected, ~1000 are expected to have full recovery and only a few will require corneal transplants (Lepkowski, 1985b).

In the months subsequent to the MIC exposure, there have been reports of an increase in stillbirths, spontaneous abortions, fetal abnormalities and infant mortality. Of an estimated 2600 pregnancies, 436 spontaneous abortions were reported during the 20 weeks following the accident. This corresponds to a rate of 16.8%, which is about twice the normal rate of 6-10% (Lepkowski, 1985b). In addition, there were 5 stillbirths and 17 cases of abnormalities among 97 delivered babies after a full-term pregnancy (Dave, 1985). These numbers are higher than the normal range. Malformations are still being studied but no obvious birth defects have been noticed (Lepkowski, 1985b). In one epidemiological study (Varma et al., 1986), 847 females were reported to have been pregnant among 3270 families surveyed. Of the 487 live births during the 9 months following the accident, 14.2% of the infants died within 30 days of birth compared with 2.6-3% infant deaths during the 2 years preceding the accident. A total of 365 pregnancies did not result in a live birth, and the loss of pregnancy was higher among women in their first trimester than in the second or third trimester. These

studies indicate that the fetal toxicity from MIC exposure is primarily due to the effects on the mother. This may be the result of general maternal and the obligatory fetal hypoxia, changes in placental blood flow, hormonal changes, damage to the placenta, as well as possible direct effects on the fetus. Spina bifida was reported as the most common fetal malformation.

Karol et al. (1986a) studied the clinical response to MIC in patients from the accident in Bhopal. MIC-human serum albumin antigens were prepared in a radioimmunoassay (ELISA) capable of detecting MIC-specific antibodies in the serum as the result of the MIC exposure. MIC antibodies were detected in 12 human serum samples out of 144 examined. These belonged to the IgG, IgM and IgE classes of antibodies. Titers were low and transient and were found in those persons having the highest MIC exposure. Antibodies were more frequently found in patients with moderate to severe clinical symptoms and in only one patient with mild symptomatology. However, to determine whether MIC has any sensitizing effects similar to those observed for TDI will require additional studies.

Karlsson et al. (1985) noted that the common characteristic of methyl isocyanate intoxication by inhalation is respiratory tract irritation. Common signs and symptoms after acute exposure to isocyanates are cough, salivation, eyelid cramping, nausea, gastritis, sweating, fever and chills. Isocyanates also serve as potent pulmonary sensitizers, inducing symptoms of bronchial asthma upon repeated exposure (Karlsson et al., 1985; Chadwick and Cleveland, 1981). Kimmerle and Eben (1964) found that inhalation exposure of volunteers to 0.9 mg/m^3 methyl isocyanate was imperceptible, 4.7 mg/m^3 was distinctly but weakly irritating to the eyes and 49.5 mg/m^3 was intolerable. Karlsson et al. (1985) considered acute exposure concentrations of 23 mg/m^3 as irritating, 68 mg/m^3 as a risk for severe injuries and 225 mg/m^3 as a risk for fatalities.

Union Carbide (1981) exposed groups of 10 male and 10 female F344 rats to methyl isocyanate vapors at concentrations of 3.07, 0.58 or 0.15 ppm (7.16, 1.35 and 0.35 mg/m^3). The rats were exposed 6 hours/day for 8 days (two periods of 4 exposure days separated by 2 days of no exposure). Compared with controls, the 3.07 ppm male and female rats had statistically significant increased relative weights of the lungs, kidneys and testes. High concentration males had reduced relative liver weights. Histopathological lesions were confined to the respiratory tract and consisted of polyploid hyperplasia of the bronchial epithelium (males only), nasal inflammation and squamous metaplasia of the nasal cavity, trachea and bronchi. Exposure to 0.58 ppm had no histological effects.

In a follow-up study, Dodd and Eisler (1983) exposed male and female F344 rats by inhalation to 0 or 3 ppm (0 or 7 mg/m^3), >99% pure methyl isocyanate. The methyl isocyanate-treated rats were divided into groups of 48/sex exposed for 8/10 days and 24/sex exposed for 4 days. The control (air-exposed) group consisted of 25 rats/sex. All rats were exposed for 6 hours/day, and survivors were sacrificed 1, 15, 43 or 85 days after exposure began.

Although no rats died during the 4- or 8-day exposure regime, ~63% of the exposed males and ~5% of the exposed females were dead by day 43. No controls died during the study. During the 8-day exposure period, there were several cases of perinasal, perioral and periocular wetness and encrustation in treated rats, and a few females had periurogenital wetness. Increased respiration and hypoactivity were common during the postexposure period. During exposure, body weights were significantly lower in the treated rats. After the exposure period, the treated female rats gained weight more rapidly than the treated males, although the weight gains of both sexes of exposed rats remained consistently below control rates.

Each rat was examined grossly upon death or sacrifice, and only the pulmonary tract was examined histopathologically. The only consistent gross lesions observed in the arts sacrificed after the last exposure day were pulmonary congestion and irritation, including inflammation and squamous metaplasia of the respiratory epithelium. Males only had submucosal fibroplasia ("polyps") of the bronchi and bronchioles and ~50% of the 8-day treated rats had pneumonitis and alveolar mucous or both. There was little involvement of lung parenchyma. In males sacrificed at 43 or 85 days post-exposure, the fibroblast-filled lesions were replaced by scar tissue characterized by mature collagen. The extent of squamous metaplasia in rats killed after 85 days was also significantly reduced, and the investigators commented that the regenerated epithelium had retrogressed through hyperplastic and hypertrophic phases to form a number of mucous plugs. The presence of these plugs probably contributed to the pneumonitis and lung discoloration observed in exposed rats sacrificed at 43 and 85 days.

Salmon et al. (1985) exposed pairs of male Lister, hooded rats to 0, 11, 21, 31 or 65 ppm (0, 26, 49, 72 or 152 mg/m^3) methyl isocyanate vapors for 2 hours. At the highest concentration, the rats had severe respiratory distress and were very sensitive to anesthesia 20 hours after exposure; one rat died 45 days after exposure and the second was sacrificed in a moribund state after 50 days. Gross observation of all tissues except the lungs revealed nothing unusual; histopathological analysis of the respiratory tract revealed hemorrhagic patches in the upper respiratory tract and fluid-filled lungs and bronchi. Prominent at intermediate concentrations was damage to the corneal epithelium, with no further involvement of the lens or internal ocular structures. At 11 ppm and particularly at 21 ppm, rats became sedated in the absence of severe respiratory depression.

Nemery et al. (1985) exposed groups of one to eight male, pentobarbital-anesthesized LAC-P rats for 1 hour to 0, 0.02, 0.1, 0.25, 0.5, 1 or for 15 minutes to 10 mg/ℓ methyl isocyanate vapors. The high concentration was lethal to 6/8 rats. Exposure to ≥0.25 mg/ℓ led to respiratory acidosis and hypoxemia; at lower concentrations, the acidosis was reversible. Breathing irregularities including decreases in breathing rates and reflexive apneic pauses between breaths were common at ≥0.1 mg/ℓ. At 1 mg/ℓ, there was complete destruction of the epithelial cells of the larynx, with prominent destruction of Type I pneumocytes, and alveolar edema and hemorrhage. Within 2 hours of exposure to 0.1-0.5 mg/ℓ, necrosis and autophagy were observed primarily in the upper airways. Damage was more extensive 1 day after exposure, but repair mechanisms had begun to take effect by 2 days. Exposure to 0.02 mg/ℓ methyl isocyanate resulted only in isolated autophagic vacuoles 24 hours after treatment. Nemery et al. (1985) concluded that methyl isocyanate was both a sensory and a pulmonary irritant, causing shallow breathing, pulmonary edema and decreased breathing rate.

In a study designed to help predict the long-term effects of a single exposure to MIC, Bucher et al. (1986) exposed F344N rats and B6C3F1 mice to concentrations of 0, 3, 10 or 30 ppm for 2 hours. Five rats and mice of each sex were killed periodically over the following 3 months for toxicologic evaluation. Clinical signs were related to irritation of the respiratory tract, i.e., shallow breathing, closed eyes and restlessness. At lethal levels, dyspnea, a pink frothy discharge from the nose, and excessive lacrimation were noted. Deaths were generally preceded by periods of respiratory distress. Deaths in rats exposed to 10 or 30 ppm and mice exposed to 30 ppm were noted beginning 12-18 hours postexposure. A majority

of the deaths occurred during the first 4 days, followed by a second period of lethality during days 8-10 postexposure. Body weight gain was decreased shortly after exposure in a dose-related manner, but after 2 weeks, the survivors gained weight at a rate equal to controls. The target organ was the respiratory tract. Lung weight increased up to 2-fold throughout the 91-day study, and epithelial necrosis accompanied with sloughing was noted from the nasal cavity to the level of the bronchioles at all concentrations. The nasal cavity showed complete repair in 28 days (Gupta et al., 1986a). Deeper portions of the respiratory tract showed reepithelization, however, peribronchial and endobronchial fibrosis developed (Brody and Hill, 1986). Compromises in pulmonary function paralleled the morphologic changes noted in the respiratory tract (Stevens et al., 1986). In another study by Ferguson et al. (1986a), male guinea pigs were exposed to concentrations of MIC between 2 and 35 ppm for 90 minutes and their pulmonary function was monitored over 21 days. At concentrations >2 ppm, the guinea pigs exhibited abnormal respiratory patterns with the maximum response occurring within 7 days following exposure. Recovery of pulmonary function and normal respiratory patterns occurred by day 21. Some animals are still on study and will be examined later for possible pulmonary fibrosis. Similar results were noted in male LAC-P rats exposed to 8, 40, 100, 200, 400 or 4000 ppm for 1 hour. In animals that survived, pulmonary function was restored in 2-3 weeks although light and electron microscopic findings revealed fibrosis and recurring foci of injury (Nemery et al., 1985).

In a cytogenetic study by Tice et al. (1986), no deaths were reported when B6C3FI mice were exposed for 30 ppm MIC for 2 hours or to 6 ppm for 6 hours/day for 4 days. Mice were sacrificed 18-30 hours postexposure.

The eyes of male and female rats exposed to 3, 10 or 30 ppm MIC were examined using fluorescein and ultraviolet light and by histopathologic examination (Gupta et al., 1986b). No significant gross or microscopic evidence of epithelial erosion or corneal ulceration was noted following exposure to 3 ppm MIC. Salmon et al. (1985) exposed rats to concentrations of MIC ranging between 11 and 65 ppm. Eye changes were confined to erosion of the corneal epithelium in rats exposed to 21 or 31 ppm while animals exposed to 65 ppm died or were sacrificed in extremis at 50 hours post-exposure.

In a report by Ferguson et al. (1986b), Swiss-Webster mice (24-28 g) were exposed to MIC concentrations of 0.5 or 7.6 ppm for 90 minutes. The index of sensory irritation, the concentration that evokes a 50% reduction in respiratory rate (RD_{50}), for MIC was 1.3 ppm. To evaluate pulmonary irritation, mice were fitted with a tracheal cannula (TC) and exposed to MIC concentrations of 0.4 or 7.3 ppm for 90 minutes. The index of pulmonary irritation, the RD_{50} TC, for MIC was 1.9 ppm.

Because the level for lung injury is about the same for sensory irritation, there is the likelihood of pulmonary injury when irritation is experienced (Alarie et al., 1986). Compared with other industrial chemicals, MIC is one of the most potent sensory irritants (Alarie and Luo, 1986).

Alarie et al. (1986) used guinea pigs to evaluate recovery from pulmonary irritation induced by MIC. Eight animals were exposed for 3 hours to 2-37 ppm MIC. To detect pulmonary responses, respiratory frequency, tidal volume and responses to 10% CO_2 were evaluated. Two animals survived exposure to 37 ppm and were used in the evaluation. Results indicated that recovery is very slow and involve deteriorating conditions during recovery.

In a separate study in which Swiss-Webster mice were exposed to MIC for 60 minutes, Karol et al. (1986b) reported an RD_{50} of 2.2 ppm for sensory irritation and an RD_{50} TC of 6.6 ppm for pulmonary irritation.

Before the Bhopal incident, limited information was available on the biochemical effects of MIC in laboratory animals. Union Carbide Corporation (1967) reported that MIC, as shown by Pozzani and Kinkead (1966), is a sensitizer of the immune system of animals; this paper, however, was not available for review. In a series of immunotoxicity studies, Silver et al. (1986) exposed female B6C3F1 mice for 6 hours to 0, 1 or 3 ppm MIC on 4 consecutive days. To evaluate immune functions over the 5 days following exposure, splenic lymphocytes were used in several established assays. These included the antibody plaque-forming cell response to sheep erythrocytes, lymphoproliferation to the polyclonal activators phytohemagglutinin, concanavalin A, lipopolysaccharide, and allogenic leukocytes, as well as natural killer cell activity. There were no remarkable changes in immune function or host resistance in mice exposed to MIC. These results have been submitted for publication (Tucker et al., 1986). In addition, Karol et al. (1986a) exposed guinea pigs to MIC in reactive form. Three weeks later, blood was drawn and the serum analyzed for antibodies to MIC using enzyme-linked immunoabsorbent assay (ELISA). To detect antibodies, an antigen was prepared by reacting MIC with guinea pig serum albumin. Analysis revealed that the antigen contained ~50 moles MIC/mole albumin. Antibodies were detected in each of the guinea pigs exposed to MIC, with titers ranging from 1:5000 to 1:10,000. Specificity for the MIC conjugate was verified using inhibition assays.

Oral and dermal LD_{50} values and inhalation LC_{50} values are provided in Table 5-1. The acute effects of methyl isocyanate inhalation exposure on

TABLE 5-1

Oral and Dermal LD_{50}s and Inhalation LC_{50}s for Methyl Isocyanate

Species	Route	LD_{50} or LC_{50}	Reference
Rat	oral	68 mg/kg	Smyth et al., 1969
Rat	oral	140 mg/kg	Vernot et al., 1977
Mouse	oral	120 mg/kg	Vernot et al., 1977
Rat	inhalation (6-hour)	6.1 ppm (14.2 mg/m^3)	Dodd et al., 1982
Mouse	inhalation (6-hour)	12.2 ppm (28.5 mg/m^3)	Dodd et al., 1982
Guinea pig	inhalation (6-hour)	5.4 ppm (12.6 mg/m^3)	Dodd et al., 1982
Rabbit	dermal	1800 mg/kg	Vernot et al., 1977
Rabbit	dermal	210 mg/kg	Smyth et al., 1969

rats, mice and guinea pigs as described in other studies (Kimmerle and Eben, 1964; Dodd et al., 1982) are similar to results already discussed.

Lee (1976) demonstrated that methyl isocyanate-treated sickle cells showed a much greater oxygen affinity than did untreated sickle cells.

5.7. SUMMARY

Pertinent data regarding the chronic or subchronic toxicity or oncogenicity of methyl isocyanate were not available. NTP (1983) found the compound not to be mutagenic in a standard reverse mutation assay, nor in a sex-linked recessive lethal test in Drosophila. In contrast, dose-related increases in SCE and CA were seen in Chinese hamster ovary cells. These increases were accompanied by cytotoxicity. A dose-dependent increase in the frequency of mutants in L5178Y cells was observed (also accompanied by cytotoxicity). Small increases in SCE and CA have been noted in mouse bone marrow following inhalation of methyl isocyanate.

Methyl isocyanate was apparently the chief etiological agent in the deaths of ~2000 people after a gas leak at a Union Carbide facility in Bhopal, India. Most of the fatalities were caused by pulmonary edema, and many survivors had symptoms of chronic lung disease (Sax, 1985). Corneal irritation was also consistently observed, but was often reversible in survivors. Other toxic manifestations in fatal cases were bright red blood, softening of the brain tissue and early rigor mortis. Indian physicians claimed that ~600 of the deaths were atypical as they were characterized by exceptionally bright red blood and absence of a panic reaction, pulmonary edema or signs of struggle (Browning, 1985a). Survivors of the Bhopal accident also suffered reproductive impairments including leukorrhea, pelvic inflammatory disease, excessive menstrual bleeding, suppression of lactation, increases in stillbirths and spontaneous abortions, and male impotence.

In addition to the severe mucous membrane irritation, isocyanates (as a class) act as pulmonary sensitizers (Karlsson et al., 1985; Chadwick and Cleveland, 1981). Short-term exposure to a concentration of 4.7 mg/m³ was weakly irritating to volunteers, whereas 49.5 mg/m³ was intolerable (Karlsson et al., 1985).

Results of acute inhalation experiments on laboratory animals have consistently shown pulmonary edema and upper respiratory tract damage after exposure to methyl isocyanate (Union Carbide, 1981; Dodd and Eisler, 1983; Salmon et al., 1985; Nemery et al., 1985; Kimmerle and Eben, 1964; Dodd et al., 1982). Rats exposed 6 hours/day for 8 days to 3 ppm (7 mg/m³) methyl isocyanate had significant increases in relative lung, kidney and testicular weights, and decreased liver weights, submucosal fibroplasia of the bronchi, pneumonitis, alveolar mucous, repair of immature fibroblasts, squamous metaplasia of the respiratory epithelium and delayed death (Union Carbide, 1981; Dodd and Eisler, 1983).

Rats exposed to 65 ppm (152 mg/m³) for 2 hours were moribund or died within 50 days of exposure, and rats exposed to 11 or 21 ppm (26 or 49 mg/m³) had pronounced narcosis (Salmon et al., 1985). Exposure of rats to 1 mg/ℓ (1000 mg/m³) for 1 hour resulted in destruction of Type I pneumocytes, alveolar edema and hemorrhage (Nemery et al., 1985). Exposure to 0.1-0.5 mg/ℓ (100-500 mg/m³) for 1 hour resulted in necrosis and autophagy of the upper airways.

Oral and dermal LD_{50} values in experimental animals have ranged from 68-140 and 210-1800 mg/kg, respectively (Smyth et al., 1969; Vernot et al., 1977). Inhalation 6-hour LC_{50} values in rats, mice and guinea pigs vary from 5.4-12.2 ppm (12.6-28.5 mg/m³) (Dodd et al., 1982). The potent anti-sickling properties of methyl isocyanate were demonstrated by Lee (1976).

6. AQUATIC TOXICITY

Pertinent data regarding effects of methyl isocyanate on aquatic organisms could not be located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The ACGIH (1985-1986) adopted an 8-hour TLV-TWA of 0.02 ppm (~0.05 mg/m^3) for methyl isocyanate. Because of the compound's potent skin irritant properties (Smyth et al., 1969), a "skin" designation was added to this value. In its documentation, the ACGIH (1986) justified this value on the basis of the reactive, irritant, corrosive and potentially sensitizing effects of methyl isocyanate. OSHA (1985) also considers 0.02 ppm to be a PEL, and has also included a skin designation.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the effects of methyl isocyanate could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Pertinent data regarding the chronic or subchronic toxicity or oncogenicity of methyl isocyanate were not available. MIC has been reported to induce mutagenic responses, in the absence of exogenous activation, in mouse lymphoma cells. Following *in vivo* exposure of mice to MIC levels of 1-30 ppm, MIC did not induce SCE levels above baseline in either bone marrow, alveolar macrophage, or peripheral blood or splenic lymphocytes. Cytotoxicity was apparent at levels in excess of 15 ppm, but cell cycle delay was observed at 3 ppm after a 4-day exposure. In other *in vivo* studies in mice, an increase in SCE was apparent at only cytotoxic doses (6 ppm). Dose-related increases in SCE and chromosal aberrations, however, were reported for Chinese hamster ovary cells.

Methyl isocyanate was apparently the chief etiological agent in the deaths of ~2000 people after a gas leak at a Union Carbide facility in Bhopal, India. Most of the fatalities were caused by pulmonary edema, and many survivors had symptoms of chronic lung disease (Sax, 1985). Corneal irritation was also consistently observed, but was often reversible in survivors. Other toxic manifestations in fatal cases were bright red blood, softening of the brain tissue and early rigor mortis. Indian physicians claimed that ~600 of the deaths were atypical as they were characterized by exceptionally bright red blood and absence of a panic reaction, pulmonary edema or signs of struggle (Browning, 1985a). Survivors of the Bhopal accident also suffered reproductive impairments including leukorrhea, pelvic inflammatory disease, excessive menstrual bleeding, suppression of lactation, increases in stillbirths and spontaneous abortions, and male impotence.

Because of the lack of defined exposure information associated with the release in Bhopal, it is not possible to construct accurate dose-response relationships. Reconstruction of exposure data based on estimates derived from effects on humans and animals suggests that the exposure level near the site of release may have been as high as 100 ppm for perhaps about 30 minutes. As the cloud spread, the estimated ground level concentration could have been as high as about 25 ppm beyond the point of release. This is about 10 times the level documented, in clinical settings, to cause pulmonary and eye irritation after 15 minutes of exposure; no irritation effects were reported at 0.4 ppm.

In addition to the severe mucous membrane irritation, isocyanates (as a class) act as pulmonary sensitizers (Karlsson et al., 1985; Chadwick and Cleveland, 1981). Short-term exposure to a concentration of 4.7 mg/m^3 was weakly irritating to volunteers, whereas 49.5 mg/m^3 was intolerable (Karlsson et al., 1985).

Results of acute inhalation experiments on laboratory animals have consistently shown pulmonary edema and upper respiratory tract damage after exposure to methyl isocyanate (Union Carbide, 1981; Dodd and Eisler, 1983; Salmon et al., 1985; Nemery et al., 1985; Kimmerle and Eben, 1964; Dodd et al., 1982). Rats exposed 6 hours/day for 8 days to 3 ppm (7 mg/m^3) methyl isocyanate had significant increases in relative lung, kidney and testicular weights, and decreased liver weights, submucosal fibroplasia of the bronchi, pneumonitis, alveolar mucous, repair of immature fibroblasts, squamous metaplasia of the respiratory epithelium and delayed death (Union Carbide, 1981; Dodd and Eisler, 1983).

Studies in laboratory animals provide additional evidence that MIC is a very potent sensory and pulmonary irritant. In mice, the level of MIC shown to reduce respiration by 50% (index for sensory irritation) is between 1 and 2 ppm. This is not greatly different than a comparable index for pulmonary irritation (between 2 and 7 ppm). This implies a likelihood of pulmonary injury when irritation is experienced.

Pulmonary dysfunction at these levels has been borne out by acute exposures of laboratory animals. When guinea pigs were exposed for 90 minutes to 2 ppm, abnormal respiratory patterns resulted, which persisted once exposure ceased. Pulmonary dysfunction as well as morphologic changes consistent with pulmonary fibrosis also were observed in mice, exposed for 120 minutes at levels of 3 ppm or greater. At 3 ppm (about one-half the LC_{50}), rats exposed for 6 hours/day for 8 days exhibited significant alterations in lung morphology; inflammatory lesions persisted in the recovery period. At exposure levels of 0.15 and 0.58 ppm, no remarkable effects were noted. In addition, ocular damage (corneal erosion) has been observed in rats at about 25 ppm during a 2-hour exposure period but not at 3 ppm.

Rats exposed to 65 ppm (152 mg/m^3) for 2 hours were moribund or died within 50 days of exposure, and rats exposed to 11 or 21 ppm (26 or 49 mg/m^3) had pronounced narcosis (Salmon et al., 1985). Exposure of rats to 1 mg/mℓ (1000 mg/m^3) for 1 hour resulted in destruction of Type I pneumocytes, alveolar edema and hemorrhage (Nemery et al., 1985). Exposure to 0.1-0.5 mg/ℓ (100-500 mg/m^3) for 1 hour resulted in necrosis and autophagy of the upper airways.

The immunological aspects of MIC exposure have not been well-characterized. It is not possible to determine the extent to which MIC exposure results in a similar pathogenesis as has been seen with other isocyanates. Antibodies to MIC have been detected in sera of some Bhopal survivors and in guinea pigs. In the only reported study in mice (female), there were no remarkable alterations in immune function or host resistence using well-established assays. In this study, exposure was conducted at 1 or 3 ppm, 6 hours/day, for 4 days.

Reproductive studies in mice, although limited, support the observations in Bhopal, that MIC can adversely affect reproduction. In pregnant Swiss-Webster mice exposed to either 9 or 15 ppm gestation, the principal effects were death (14% of dams) and complete resorption of the litter in 75% of the dams. Although no organ abnormalities were observed, fetal body weights and skeletal size was diminished. MIC was more toxic to dams when exposed on day 14 of gestation (64% mortality). Effects were less pronounced at 2 and 6 ppm. An exposure level of 9 ppm was identified as affecting the estrus cycle and the fertility of both male and female mice.

Decreased neonate survival, as well as decreased live litter size at birth, were the principal findings when CD-1 mice were exposed on gestation days 14 to 17 (hours/day) to 1 or 3 ppm MIC. Maternal survival was unaffected. There were no reported effects on reproductive capacity of male or female mice at these levels.

Because of the brief nature of these reports and the unavailability of protocol details and test data, it is not possible to fully evaluate the potential reproductive effects of MIC exposure.

Oral and dermal LD_{50} values in experimental animals have ranged from 68-140 and 210-1800 mg/kg, respectively (Smyth et al., 1969; Vernot et al., 1977). Inhalation 6-hour LC_{50} values in rats, mice and guinea pigs vary from 5.4-12.2 ppm (12.6-28.5 mg/m^3) (Dodd et al., 1982). The potent anti-sickling properties of methyl isocyanate were demonstrated by Lee (1976).

The lack of pertinent data regarding carcinogenicity, and chronic or subchronic toxicity of methyl isocyanate, precludes derivation of a q_1^* or RfD.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Pertinent data regarding oral or inhalation subchronic or chronic toxicity of methyl isocyanate could not be located; therefore, data are not sufficient for deriving an RQ (Table 9-1)

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

No data could be located regarding the carcinogenicity of methyl isocyanate in animals and humans in the available literature. Therefore, methyl isocyanate is classified as a Group D chemical using EPA's carcinogen risk assessment guidelines.

TABLE 9-1

Methyl Isocyanate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	
Dose:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data are not sufficient for deriving an RQ.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

GLOBAL
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in April, 1986. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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